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EXAMINER	
OLSON, ERIC	

ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/693,794	ZELDIS ET AL.	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8,9,15,16 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8,9,15,16 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 7/26/04, 6/6/05, 1/3/06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This application claims benefit of provisional application 60/421003, filed October 24, 2002.

Applicant's amendment submitted September 15, 2006 is acknowledged wherein claims 7, 10-14, 17-22, and 24-26 are cancelled, and claims 6 and 8 are amended.

Election/Restrictions

Applicant's election with traverse of group II, drawn to a method of treating neuropathic pain, filed September 15, 2006, is acknowledged. Applicant's arguments of record with respect to the aforementioned traversal are acknowledged and not found to be persuasive to remove the requirement for restriction. Applicant asserts that a search for methods of treating both neuropathic and nociceptive pain would not impose an undue burden because a search for all reference mentioning the claimed compounds will necessarily turn up all possible uses for those compounds. This argument is not found to be persuasive because, as mentioned in the requirement for restriction, the search for a compound is not co-extensive with the search for a method of using that compound. A search of the literature for a compound will uncover many references with no relevance to the patentability of a particular method of using that compound. Furthermore, a search and thorough reading of all references relating to a compound would not be sufficient to determine the patentability of a particular method of using that compound, as there may exist additional references which, though not containing an

explicit reference to the compound, will when considered in combination with the literature explicitly mentioning said compound, render a particular method of using the compound obvious. For this reason, restriction between product and process claims, and between different methods of using the same product, is considered to be proper when the different inventions either not capable of use together or can have a materially different design, mode of operation, function, or effect. As mentioned in the previous requirement for restriction, the effects of the two inventions are quite different as nociceptive and neuropathic pain are recognized in the art as being very different diseases with different causes, pathology, and treatments, linked only by being painful. For these reasons the requirement for restriction is deemed proper and made **FINAL**.

Applicant's election of specific compound and disease species is acknowledged. The requirement for election of species is withdrawn. All species claimed in group I will be examined in the merits.

Claims 1-6, 8-9, 15-16, and 23 are pending in this application and examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 8-9, 15, 16, and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating neuropathic pain, does not reasonably provide enablement for a method of preventing or modifying pain, or administering a prophylactically effective amount of a second agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is drawn to a therapeutic method for treatment or prevention of a disorder.

The state of the prior art: Cytokines such as TNF-alpha possess multiple biological effects, not all of which have been fully characterized. Inhibitors of these compounds are known to exert analgesic effects against pain, including neuropathic pain. In addition, many other compounds also possess immunomodulatory effects. These analgesic effects are temporary, and no permanent effects on the subject's

nervous system have been reported. Drugs which exhibit a permanent curative analgesic effect (i.e. permanently relieving a painful syndrome) are not known, except in cases where the relief of pain is a secondary effect to the permanent cure of the underlying disease (e.g. pain caused by cancer or microbial infection). Similarly, there is no precedent in the prior art for any immunomodulatory drug which is capable of permanently preventing the occurrence of pain after the drug is cleared from the patient's system. Similarly, no drug could permanently prevent the occurrence of all pathological conditions having neuropathic pain as a symptom, as many of these conditions (e.g. postsurgical pain, phantom limb syndrome) arise from physical trauma to the nervous system and no drug is capable of preventing physical trauma.
In fact, no mechanism is known by which drugs of the kind described in the claimed invention could exert any analgesic effects after being cleared from a subject's system, as they must generally be present within the subject's body in order to be effective. Furthermore, it is generally desired within the art that an analgesic treatment not exert permanent effects on a patient's nervous system, as such permanent effects may very well be deleterious, particularly if the biological target being affected is an important, multifunctional target such as the immune system.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: There are many different syndromes which may lead to neuropathic pain as one symptom. According to the Merck Manual of Diagnosis and Therapy, 17th edition (Reference included with PTO-892) neuropathic pain may be caused by multiple underlying causes, generally

classified as either deafferentiation pain or sympathetically maintained pain. (p. 1371, right column, third paragraph) Specific syndromes causing neuropathic pain include, but are not limited to postherpetic neuralgia, phantom limb pain, root avulsions, painful traumatic neuropathy, painful polyneuropathy, central pain syndromes, postsurgical pain syndromes, and postthoractomy syndrome. (p. 1372, left column, 4th paragraph) Furthermore, it is stated that, "Treatment applied without concern for diagnosis, rehabilitation, and psychosocial issues has a limited chance of success." (p. 1372, left column, 3rd paragraph) Thus a treatment that is prophylactic or curative for one particular neuropathic pain syndrome is unlikely to thus be curative for every neuropathic pain syndrome, as a cure or prevention would involve the permanent reversal or prevention of the underlying syndrome rather than the temporary relief of painful symptoms. Furthermore, it is very difficult to predict who will develop a particular neuropathic pain syndrome and when.

In addition, prevention of a disease is not the same as treatment of said disease. In order to prevent a disease, as opposed to merely delaying or reducing its symptoms, a treatment must either render the subject completely resistant to said disease after a single treatment or a limited number of treatments, or else, when continued indefinitely, continue to completely suppress the occurrence of said disease. In order to practice a preventative method, one of skill in the art must know the answer to several questions in addition to the effectiveness of the therapy in short-term relief of symptoms, including:

1) What is the duration of a single course of therapy? How often must the therapy be administered to completely suppress the disease?

2) Does the subject develop tolerance to the therapy over time? Does the disease eventually progress to a point where the therapy is unable to completely suppress all symptoms? For example, will a metastatic cancer eventually adapt to overcome treatments directed to preventing it from metastasizing into the bone? Or will a case of osteoporosis or rheumatoid arthritis ultimately progress to a point where symptoms develop regardless of which therapy is administered.

3) What are the long-term effects of the therapy? Does it cause progressive damage to the kidneys, liver, or other organs? Does the active agent accumulate in the subject's tissues? Is the minimum dose necessary to completely prevent the disease safe for long-term administration? Are there any steps that can be taken to reduce side effects?

For this reason, many therapies which are suitable for short-term relief of symptoms are not suitable for lifelong prevention of disease. For example, antibiotics, chemotherapeutics, and antiviral drugs are not normally administered to healthy subjects in order to prevent the development of infection or cancer.

The Breadth of the claims: In the absence of an explicit definition in Applicant's specification, "Prevention" as recited in the instant claims, is interpreted to mean the complete and total blocking of all symptoms of a disorder for an indefinite period of time. Any therapy which merely reduces the number or severity of symptoms, or which is effective for a period shorter than the subject's remaining lifespan, is considered to be ineffective at preventing a disorder. A prophylactically effective amount of a therapeutic agent is an amount which is sufficient to exert a preventative effect. Modifying pain is

interpreted to mean decreasing or increasing pain, altering the character of the pain, preventing future occurrence of pain, or exerting any other effect whatsoever against a painful condition.

The amount of direction or guidance presented: A number of compounds which are capable of treating neuropathic pain by modulating the immune system. None of these compounds are disclosed as being suitable for prevention of neuropathic pain.

The presence or absence of working examples: No working examples are provided for a method of preventing neuropathic pain.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the prevention of pain. See MPEP 2164.

The quantity of experimentation necessary: Based on the state of the prior art, one skilled in the art would believe that the only way to permanently cure a case of neuropathic pain is to remove the underlying cause. Similarly, the only way to permanently prevent neuropathic pain is to permanently prevent every disorder having neuropathic pain as a symptom. A cure is possible in certain instances, such as surgical decompression of carpal tunnel syndrome. Other forms of neuropathic pain, such as that arising from phantom limb syndrome, cannot be permanently cured or prevented and must be treated through palliative means. The applicant's disclosure does nothing to challenge this conclusion. Although the applicant discloses a pharmaceutical composition which is potentially useful for the palliative treatment of

neuropathic pain, nothing in the disclosure suggests that there exists any method by which the claimed composition would be useful for the prevention of neuropathic pain.

In order to practice the claimed invention for the curative or prophylactic treatment of neuropathic pain, one skilled in the art would need to independently develop curative and preventative therapies for a variety of disorders, including but not limited to those recited previously. It is unlikely that every such syndrome would be adequately cured or prevented by a pharmaceutical treatment. Rather, certain treatments would involve surgery and/or physical therapy as an essential component for the cure or prevention of neuropathic pain. Developing such therapeutic methods in the absence of any guidance from applicant's disclosure constitutes undue experimentation. Thus the applicant's disclosure is not enabling for the curative or prophylactic treatment of pain, particularly neuropathic pain.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the state of the prior art and the lack of guidance or working examples, Applicants fail to provide information sufficient to practice the claimed invention for the prevention or modification of neuropathic pain, or for a method comprising administering a prophylactically effective amount of a second active agent.

Claims 1-6, 8-9, and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating neuropathic pain by administering specific cytokine inhibitory drugs such as the compound disclosed in instant claim 27, does not reasonably provide enablement for such a method involving any selective cytokine inhibitory drug whatsoever. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a therapeutic method involving administering to a patient an immunomodulatory drug.

The state of the prior art: The prior art discloses that a variety of immunomodulatory drugs are used for the treatment of pain, including both nociceptive and neuropathic pain. The prior art does not disclose that all immunomodulatory drugs are generally useful for the treatment of neuropathic pain.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: There are many different syndromes which may lead to neuropathic pain as one symptom. According to the Merck Manual of Diagnosis and Therapy, 17th edition (Reference included with PTO-892) neuropathic pain may be caused by multiple underlying causes, generally classified as either deafferentiation pain or sympathetically maintained pain. (p. 1371, right column, third paragraph) Specific syndromes causing neuropathic pain include, but are not limited to postherpetic neuralgia, phantom limb pain, root avulsions, painful traumatic neuropathy, painful polyneuropathy, central pain syndromes, postsurgical pain syndromes, and postthoractomy syndrome. (p. 1372, left column, 4th paragraph) Furthermore, it is stated that, "Treatment applied without concern for diagnosis, rehabilitation, and psychosocial issues has a limited chance of success." (p. 1372, left column, 3rd paragraph) Thus the treatment of neuropathic pain is highly unpredictable.

The Breadth of the claims: The claimed invention is very broad, including therapeutic methods involving any conceivable immunomodulatory drug. The term "immunomodulatory compound" is defined on p. 13, lines 23-26 to refer to compounds which inhibit cytokine production, particularly production of TNF-α.

The amount of direction or guidance presented: Applicant's specification discloses that compounds having a certain general range of structures can treat neuropathic pain by inhibiting TNF-alpha, and also discloses s number of experimental protocols by which this activity may be measured. Applicant does not disclose any method for determining the full scope of compounds with this activity or synthesizing all of them.

The presence or absence of working examples: A number of specific compounds are disclosed which are useful in the claimed invention. These compounds are not representative of the full range of possible selective cytokine inhibitors which could be imagined.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the treatment of neuropathic pain. See MPEP 2164.

The quantity of experimentation necessary: One of ordinary skill in the art, in order to practice the claimed invention with the full range of immunomodulatory compounds beyond the meager number disclosed in the specification would be required to test potential compounds *in vivo* to determine whether a particular compound is useful as an immunomodulatory compound. According to the 2006 Chemical Abstracts catalog, The Chemical Abstracts Registry contains entries for approximately 26 million compounds, all of which are potentially included in the claimed invention if they happen to have immunomodulatory activity. For most compounds, it is unknown whether they are or are not useful in this manner. Gathering this data for every compound known to man would involve *in vitro* screening of an enormous diversity of chemical compounds for immunomodulatory activity, as well as *in vivo* testing of compounds having this activity involving either human or animal subjects to determine therapeutic utility. *In vitro* testing requires that the compounds to be tested be synthesized and subjected to an appropriate screening method. Synthesis of diverse chemical structures requires novel and unpredictable experimentation in order to develop suitable synthetic methods.

In vivo animal experiments include, along with induction of the disease state, administration of the potential pharmaceutical compound and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Human tests impose even greater ethical and regulatory burdens, as well as additional difficulty locating subjects. Because of the unpredictability of the art and the lack of comprehensive working examples covering any significant portion of the total number of potential immunomodulatory compounds, these animal experiments would need to be repeated hundreds of times, and involve the maintenance, killing, dissection, and disposal of thousands of experimental animals, to establish the activity or lack thereof of every possible immunomodulatory compound, thus presenting an a burden of undue experimentation to anyone practicing the invention with the full range of immunomodulatory compounds claimed.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the scope of the claims and the lack of guidance or working examples, Applicants fail to provide information sufficient to practice the claimed invention for each and every possible immunomodulatory compound.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 6, 8, and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Rajkumar et al. (Reference included with PTO-1449) Rajkumar et al. discloses a case study of a patient suffering from reflex sympathetic dystrophy (complex regional pain syndrome type I) whose symptoms improved after treatment with thalidomide. (p. 2502, right column, second paragraph) Thalidomide is an immunomodulatory drug which selectively inhibits TNF-α synthesis. (for example, see George et al., reference included with PTO-1449, p. 267, right column, second paragraph) This case is thus a method of treating complex regional pain syndrome according to instant claims 1, 6, 8, and 9. The claimed invention is thus anticipated by Rajkumar et al.

Claims 1, 6, and 15 are rejected under 35 U.S.C. 102(e) as being anticipated by Olmarker et al. (PCT international publication WO02080891, included with PTO-892) Olmarker et al. discloses a method of treating low back pain due to leakage of the

nucleus pulposus from a damaged intravertebral disk, comprising administering a TNF inhibitor. (pp. 4-6) Because the mechanism of this pain involves the irritation of an affected nerve, it is considered to be a form of neuropathic pain. Specific compounds useful in the method of Olmarker et al. include thalidomide derivatives, including the compound CDC-501, which according to its chemical abstracts registry entry, is identical to the immunomodulatory compound 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione of instant claim 15. Olmarker et al. thus anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2-5 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rajkumar et al. (Reference included with PTO-1449) in view of the Merck manual of diagnosis and therapy, seventeenth edition. (Herein referred to as Merck, reference included with PTO-892)

The disclosure of Rajkumar et al. is discussed above. Rajkumar et al. does not disclose a method further comprising administering the additional therapeutic agents of instant claims 2-5 or the therapies of instant claim 23.

Merck discloses that complex regional pain syndrome may be treated with several drugs including nifedipine, prednisone, opioid analgesics, tricyclic antidepressants, and anticonvulsants. (p. 1373, left column, second paragraph) It should be noted that it is well known in the art that opioid analgesics include oxycodone, tricyclic antidepressants include amitryptyline, imipramine, and doxepin, and anticonvulsants include gabapentin. Merck also discloses that physical therapy is essential throughout therapy for complex regional pain syndrome (p. 1373, left column, last paragraph) and that pain relief that outlasts the administration of a sympathetic block but is still transitory suggests the need for surgery. (p. 1373, left column, second paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the method of Rajkumar et al. for the treatment of complex regional pain syndrome further comprising administering one or more of the pharmaceutical active agents described by Merck and still further administering physical therapy and/or surgery. One of ordinary skill in the art would have been motivated to combine these teachings because Rajkumar et al. and Merck both disclose their respective teaching as being useful for treating the same condition, namely complex regional pain syndrome. One of ordinary skill in the art would reasonably have expected success because combining two treatments known in the prior art to be effective for treating the same disorder by different methods is reasonably expected to produce at least additive effects.

Thus the invention taken as a whole is *prima facie* obvious.

Claims 2-5 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Olmarker et al. (PCT international publication WO02080891, included with PTO-892) in view of the Merck manual of diagnosis and therapy, seventeenth edition. (Herein referred to as Merck, reference included with PTO-892)

The disclosure of Olmarker et al. is discussed above. Olmarker et al. does not disclose a method further comprising administering the additional therapeutic agents of instant claims 2-5 or the therapies of instant claim 23.

Merck discloses that therapies effective for the treatment of low back pain (of which the pain arising from nucleus pulposus leakage is a subset, include oral analgesics such as asprin, as well as muscle relaxants, and, in the case of chronic low back pain, anti-inflammatory steroids such as dexamethasone acetate, methylprednisone acetate, hydrocortisone acetate, or triamcinolone acetate. (p. 477, right column, last paragraph – p. 478, left column ,third paragraph) Merck also discloses that physical therapy is indicated for chronic low back pain, (p. 478, left column, second paragraph) and that surgery may be necessary in the case of disk disease. (p. 478, left column, fourth paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the method of Olmarker et al. further comprising administering one or more of the pharmaceutical active agents described by Merck and still further administering physical therapy or surgery as appropriate. One of ordinary skill in the art would have been motivated to combine these teachings because Olmarker et al. and

Merck both disclose their respective teaching as being useful for treating the same condition, namely low back pain. One of ordinary skill in the art would reasonably have expected success because combining two treatments known in the prior art to be effective for treating the same disorder by different methods is reasonably expected to produce at least additive effects.

Thus the invention taken as a whole is *prima facie* obvious.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Olmarker et al. (PCT international publication WO02080891) in view of Remington. (Reference included with PTO-892)

The disclosure of Olmarker et al. is discussed above. Olmarker et al. does not disclose a method comprising administering the compound of claim 15 in an enantiomerically pure form.

Remington discloses that different enantiomers of the same compound may possess different biological and pharmacological activities. (pp. 462-463)

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the invention of Olmarker using enantiomerically pure 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione. One of ordinary skill in the art would have been motivated to practice the invention in this manner because, as Remington discloses that the two enantiomers of a chiral compound possess different activities *in vivo*, it stands to reason that one of the two enantiomers of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione possesses better activity and/or

reduced side effects compared to the other enantiomer, and is thus a better drug in its enantiomerically pure form. One of ordinary skill in the art would reasonably have expected success because testing two enantiomers for a known activity to determine which is the best drug candidate is a small and routine experimental burden well within the ordinary level of skill in the art.

Thus the invention taken as a whole is *prima facie* obvious.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 6, and 15 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over either claims 1 and 4 of U.S. Patent No. 5635517 (Reference cited in PTO-1449, herein referred to as '517) or alternately claims

1, 5, 9, 22, and 23 of U.S. Patent No. 5955476 (Reference cited in PTO-1449, herein referred to as '476) in view of claims 1, 21, and 27 of US patent 6635250. (Reference cited in PTO-8144992, herein referred to as '250) Claims 1 and 4 of '517 and claims 1, 5, 9, 22, and 23 of '476 are drawn to methods of reducing undesirable levels of TNF-α in a mammal by administering a compound having a the structure recited in instant claim 15. Said claims do not disclose a method of treating neuropathic pain in this manner.

Claims 1, 21, and 27 of '250 are drawn to a method of treating a nerve disorder involving pain (i.e. neuropathic pain) caused by a herniated disk by administering a TNF-α inhibitor.

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the methods of claims 1 and 4 of '517 and claims 1, 5, 9, 22, and 23 of '476 on a mammal suffering from neuropathic pain caused by a herniated disk. One of ordinary skill in the art would have been motivated to practice the invention in this manner because claims 1, 21, and 27 of '250 disclose that blocking the action of TNF-α is an effective strategy for treating neuropathic pain in a herniated disk. One of ordinary skill in the art would have reasonably expected success because claims 1, 21, and 27 of '250 already demonstrate the utility of this method.

Claims 1 and 6 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over any of the following claims:

Claim 17 of 6020358

Claim 15 of 6011050

Claim 7 of 5798368

Claim 31 of 5698579

Claims 1-12 of 5736570

Claims 14-15 of 5703098

Claim 12 of 6395754

Claim 10 of 6180644

Claims 7 and 9 of 6130226

Claim 6 of 6075041

Claims 1-2 of 6214857

Claims 8 and 11 of 5968945

in view of claims 1, 21, and 27 of US patent 6635250. (Reference cited in PTO-892, herein referred to as '250) The aforementioned are all drawn to methods of reducing undesirable levels of TNF-α in a mammal. Said claims do not disclose a method of treating neuropathic pain in this manner.

Claims 1, 21, and 27 of '250 are drawn to a method of treating a nerve disorder involving pain (i.e. neuropathic pain) caused by a herniated disk by administering a TNF-α inhibitor.

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the methods of the aforementioned claims on a mammal suffering from neuropathic pain caused by a herniated disk. One of ordinary skill in the art would have been motivated to practice the invention in this manner because claims 1, 21, and 27 of '250 disclose that blocking the action of TNF-α is an effective strategy for treating

neuropathic pain in a herniated disk. One of ordinary skill in the art would have reasonably expected success because claims 1, 21, and 27 of '250 already demonstrate the utility of this method.

Summary

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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